产品名称：Dabrafenib (GSK2118436)
产品别名：Dabrafenib；达拉非尼

生物活性：

Description	Dabrafenib is an ATP-competitive inhibitor of **Raf** with **IC_{50}**s of 5 nM and 0.6 nM for **C-Raf** and **B-Raf^{V600E}**, respectively.

IC_{50} & Target	BRaf^{V600E}	CRAF
	0.6 nM (IC_{50})	5 nM (IC_{50})

In Vitro	Dabrafenib (GSK2118436, 1 μM) with 0.01 μM GSK1120212 inhibits more than 90% of cell growth in the NRAS mutant clones. GSK2118436 is sufficient to reduce S6P phosphorylation in A375[1]. Dabrafenib suppresses the PolyP-mediated vascular barrier permeability, upregulation of inflammatory biomarkers, adhesion/migration of leukocytes, and activation and/or production of nuclear factor-κB, tumor necrosis factor-α, and interleukin-6[2]. Dabrafenib inhibits the release of HMGB1 and downregulates HMGB1-dependent inflammatory responses by enhancing the expressions of cell adhesion molecules (CAMs) in human endothelial cells[3].
In Vivo	Dabrafenib-treated females have mostly immature reproductive tracts with no evidence of ovulation, similar to age-matched controls; however, DAB-treated females have keratinized and histologically open vaginas[5].

Solvent&Solubility

In Vitro:

DMSO : ≥ 33 mg/mL (63.52 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	**1 mg**	**5 mg**	**10 mg**
	1 mM	1.9247 mL	9.6235 mL	19.2471 mL
	5 mM	0.3849 mL	1.9247 mL	3.8494 mL
	10 mM	0.1925 mL	0.9624 mL	1.9247 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (4.81 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.81 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)

	Solubility: ≥ 2.5 mg/mL (4.81 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.81 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.81 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.81 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Greger JG, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther, 2012, 11(4), 909-920. [2]. Lee S, et al. Anti-inflammatory effects of dabrafenib on polyphosphate-mediated vascular disruption. Chem Biol Interact. 2016 Jul 22. [3]. Jung B, et al. Anti-septic effects of dabrafenib on HMGB1-mediated inflammatory responses. BMB Rep. 2016 Apr;49(4):214-9. [4]. Alexander M Menzies, et al. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther. 2012; 6: 391–405. [5]. Posobiec LM, et al. Early Vaginal Opening in Juvenile Female Rats Given BRAF-Inhibitor Dabrafenib Is Not Associated with Early Physiologic Sexual Maturation. Birth Defects Res B Dev Reprod Toxicol. 2015 Dec;104(6):244-52.

实验参考：

Cell Assay	For longer term proliferation assays, cells are plated and treated with compound or combination of compounds in RMPI-1640 containing 10% FBS for 12 days. Compound treatments are replaced at least once during the assay. After 12 days, cells are stained with 0.5% methylene blue in 50% ethanol. Images are captured using flatbed scanner. [1]
Animal Administration	The rat pups selected as the test system are derived from 26 10-week-old, time-mated, virus-antibody-free SD (Crl:CD[SD]) female rats. Mated females are observed for natural deliveries from Day 20 to 23 pc (day parturition completed is designated PND 0). Litter examinations are conducted when parturition is complete, on PNDs 3 and 6, and included gender identification, individual pup weights, and external morphologic examinations. Parturient dams and their litters are selected for study based on clinical signs and body weights, and selected dams and their litters are randomized into study groups based on clinical observations and PND 3 litter mean body weights. On PND 3 or 4, litters are culled to four males and five females, with minimal fostering only when necessary to obtain the desired sex ratio, such that natural litters are maintained as much as possible. Records are kept of fostered pups of original and foster dams. All pups are identified by paw tattoo. To the extent possible, nonlittermates are assigned to subsets. DAB is formulated as a suspension in vehicle, 0.5% hydroxypropylmethylcellulose K15M, and 0.1% (v/v) Tween80 in purified water, and is given to juvenile male and female rats orally by gavage at a dose volume of 5 ml/kg, based on daily body weight. [5]
	[1]. Greger JG, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired

References	resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther. 2012, 11(4), 909-920. [2]. Lee S, et al. Anti-inflammatory effects of dabrafenib on polyphosphate-mediated vascular disruption. Chem Biol Interact. 2016 Jul 22. [3]. Jung B, et al. Anti-septic effects of dabrafenib on HMGB1-mediated inflammatory responses. BMB Rep. 2016 Apr;49(4):214-9. [4]. Alexander M Menzies, et al. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther. 2012; 6: 391–405. [5]. Posobiec LM, et al. Early Vaginal Opening in Juvenile Female Rats Given BRAF-Inhibitor Dabrafenib Is Not Associated with Early Physiologic Sexual Maturation. Birth Defects Res B Dev Reprod Toxicol. 2015 Dec;104(6):244-52.